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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/525,410	01/26/2005	Zixia Feng	2345F USA	8315

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EXAMINER	
CHENG, KAREN	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,410	FENG ET AL.	
	Examiner	Art Unit	
	Karen Cheng	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 3-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 8/8/05.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16 are currently pending in the instant application.

Priority

The application is a 371 of International Application No. PCT/US02/39316, filed on 12/09/2002, which claims the benefit of priority under 35 U.S.C. 119, to U.S. Provisional Application No. 60/343,378, filed on 12/20/2001.

Information Disclosure Statement

Applicant's Information Disclosure Statement filed on 08/08/05 has been considered. Please refer to Applicant's copies of the 1449 submitted herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for lowering intraocular pressure, does not reasonably provide enablement for providing neuroprotection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to utilize the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

The nature of the invention is directed to the administration of a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically active amount of the compound of the formula as a method for providing (ocular) neuroprotection, and a composition further comprising "at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics" as well as "at least one agent selected from the group consisting of calcium channel blockers and NMDA antagonists."

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can provide neuroprotection). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that that contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its fact.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute

According to Levin, neuroprotection is defined as a set of therapeutic strategies for the prevention of neuronal death after injury. Additionally most optic neuropathies do not have viable treatments at present. Key points to be addressed in defining neuroprotection are that neuroprotection is a therapeutic strategy, relates to the prevention of neuronal death and is a therapy used in response to any injury. Finally in order for a neuroprotective strategy to work, it must maintain the neuronal integrity of the cell and its function. Levin concludes that although cell culture and animal studies support the concept that neuroprotective therapies may prevent retinal ganglion cell death, these data by themselves are insufficient to prove clinical efficacy. Instead a randomized clinical trial needs to be completed in a neuro-ophthalmic disease before conclusions can be drawn.

Applicants have not provided any competent evidence or disclosed test results that are highly predictive for the pharmaceutical use of neuroprotection. Hence, one of skill in the art is unable to fully predict possible preventive results from the administration of the claimed compound due to the absence of convincing evidence that said composition has a preventive effect on neuronal cells after injury.

With regards to the pharmaceutical composition further comprising "at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics" as well as "at least one agent selected from the group consisting of calcium channel blockers and NMDA antagonists," the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to pharmaceutical compositions comprising multiple active agents, one would need to consider drug-drug interactions. For the preparation of pharmaceutical compositions containing multiple active ingredients, one needs to take into account drug-drug interactions. As found in Drugs of Today 39(5), 2003, 301-38, Obach discloses that in regards to any given pharmacokinetic drug-drug interaction, the two drugs involved can be considered as either the "perpetrator" drug or the "victim" drug. The perpetrator is the drug that affects the activity of an enzyme of protein involved in the metabolism or disposition of the victim drug. The victim drug is the one that either causes side-effects or toxicity due to increased exposure, or lack of efficacy due to exposure decreased to below that required for therapeutic effect (page 302). There are varying mechanisms of drug interactions such as the reduction in the rate of the metabolism of one drug by another, the irreversible inactivation of drug-metabolizing enzymes, and the exposure to the victim drug is decreased (pages 303-304). Obach also discloses that there are a number of in vitro and in vivo experimental approaches to be taken to determine drug-drug interactions (page 304).

Additionally because there are a wide range of β-blockers, prostaglandins, carbonic anhydrase inhibitors, miotics, calcium channel blockers and NMDA

antagonists, it is not known what can be encompassed by this definition unless the compound is explicitly described in the instant specification.

The amount of direction or guidance present and the presence or absence of working examples

The specification does not provide any examples of neuroprotective effects of the compound. On p. 20, test results showing the lowing of intraocular pressure are disclosed. On p. 9, it is stated that compounds falling in categories, such as β-blockers, prostaglandins, carbonic anhydrase inhibitors, miotics, can treat glaucoma but the specification does not state and fails to define the term or teach exactly what compounds can be considered "β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics" as well as "calcium channel blockers and NMDA antagonists."

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically, the instant claims include neuroprotection but the specification only provides evidence for lowering intraocular pressure using the claimed compound. The specification also does not provide direction or give examples of compounds or agents that would be considered β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics as well as calcium channel blockers and NMDA antagonists.

The quantity or experimentation needed and the level of skill in the art

It would require undue experimentation of one of ordinary skill in the art to ascertain the effectiveness of the compound in neuroprotection and to ascertain what the second compound of the composition could be. Factors such as "sufficient working

examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention and unpredictability of providing neuroprotection and drug-drug interactions, as well as the lack of working examples regarding the activity as claimed, one skilled in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in cope with the claims.

In consideration of each of the 8 factors, it is apparent that undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue. Therefore, claims 3-16 are rejected under 35 U.S.C. § 112, 1st paragraph. This rejection can be overcome by deleting the phrase providing (ocular) neuroprotection from claims 3 and 5, and canceling claims 15 and 16.

Claim Rejections - 35 USC § 112 – 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 15-16 recite the limitation "at least one agent selected from the group consisting of β-blockers, prostaglandins, carbonic anhydrase inhibitors, and miotics" as well as "at least one agent selected from the group consisting

of calcium channel blockers and NMDA antagonists." On p. 9 of the specification, it is stated that compounds falling in these categories can treat glaucoma but the specification does not state and fails to define the term or teach exactly what compounds can be considered "β-blockers, prostaglandins, carbonic anhydrase inhibitors, miotics, calcium channel blockers and NMDA antagonists." Thus, "at least one agent selected from the group" is not defined in the claims so as to know the metes and bounds of the claims. Therefore claims 15-16 are rejected.

Conclusion

A search was made of the prior art, and the closest art was found in Journal of Medicinal Chemistry, 1996, Vol. 39, No. 15, p. 2954 whereby a similar compound that has an amino alkyl chain in place of the imidazoline ring is disclosed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cheng whose telephone number is 571-272-6233. The examiner can normally be reached on M-F, 9AM to 5:30PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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